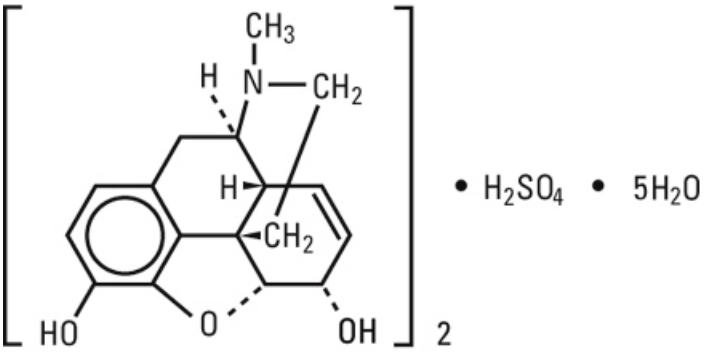
MORPHINE SULFATE - morphine sulfate injection, solution
Hospira, Inc.

CII
R_x only
WARNING: MAY BE HABIT FORMING.
PCA Vial
Protect from light
ONLY FOR USE WITH A COMPATIBLE HOSPIRA PCA PUMP SET WITH INJECTOR AND A COMPATIBLE HOSPIRA INFUSION DEVICE.

DESCRIPTION

Morphine, the most important alkaloid of opium, is classified pharmacologically as a narcotic analgesic. Morphine Sulfate, USP (pentahydrate), is chemically designated 7, 8-didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1) (salt), pentahydrate, a white crystalline powder, soluble in water. It has the following structural formula:



Preservative-free Morphine Sulfate Injection, USP, is a sterile, nonpyrogenic solution of morphine sulfate in water for injection. This product was designed to be administered by the intravenous route with a compatible Hospira infusion device.
For 0.5 mg or 1 mg presentation, each mL contains morphine sulfate, USP (pentahydrate) 0.5 mg or 1 mg, respectively, and sodium chloride, USP, 9 mg in water for injection, USP. May contain sodium hydroxide and/or hydrochloric acid for pH adjustments.
For 5 mg presentation, each mL contains morphine sulfate, USP (pentahydrate), 5 mg, sodium chloride, USP, 7.6 mg, with citric acid, USP, anhydrous 0.4 mg and sodium citrate, USP, dihydrate 0.2 mg added as buffers in water for injection, USP. May contain additional citric acid and/or sodium citrate for pH adjustment. The pH range for all preservative-free Morphine Sulfate Injection, USP presentations is 2.5 to 6.5. Morphine Sulfate Injection, USP, contains no antioxidant, bacteriostatic or antimicrobial agent, and is intended only as a single-dose unit, to provide analgesia via the intravenous route, using a compatible Hospira infusion device. Each vial is intended for SINGLE USE ONLY. When the dosing requirement is completed, the unused portion should be discarded in an appropriate manner.
DO NOT HEAT STERILIZE. Do not use the injection if its color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate.

CLINICAL PHARMACOLOGY

Morphine produces a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, and physical dependence. Opiate analgesia involves at least three anatomical areas of the central nervous system: the periaqueductal-periventricular gray matter, the ventromedial medulla, and the spinal cord. A systemically administered opiate may produce analgesia by acting at any, all, or some combination of these distinct regions. Morphine interacts predominantly with the μ-receptor. The μ-binding sites of opioids are very discretely distributed in the human brain, with high densities of sites found in the posterior amygdala, hypothalamus, thalamus, nucleus caudatus, putamen, and certain cortical areas. They are also found on the terminal axons of primary afferents within laminae I and II (substantia gelatinosa) of the spinal cord and in the spinal nucleus of the trigeminal nerve.

Pharmacokinetics

Morphine has an apparent volume of distribution ranging from 1 to 4.7 L/kg after intravenous dosage. Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. When morphine is introduced outside of the CNS, plasma concentrations of morphine remain higher than the corresponding CSF morphine levels.
Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h (liters/kilogram/hour) in postoperative patients, but shows considerable interindividual variation. The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10% in the feces. Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Terminal half-life is commonly reported to vary

from 1.5 to 4.5 hours, although the longer half-lives were obtained when morphine levels were monitored over protracted periods with very sensitive radioimmunoassay methods. The accepted elimination half-life in normal subjects is 1.5 to 2 hours.
The minimum analgesic morphine plasma concentration during Patient-Controlled Analgesia (PCA) has been reported as 20-40 ng/mL, corresponding to a self-administration rate of 1.5 to 3 mg/h.

Clinical Trials
Morphine is the most frequently-used opioid administered by PCA, and has been studied in controlled clinical trials in both acute postoperative settings and the chronic pain of malignancy. PCA morphine was administered to opioid-naive postoperative patients using a 1-2 mg bolus size and a six minute lockout interval. This resulted in an average self-administration rateof 2-3 mg/h, and average blood level of 30-70 ng/mL, and an analgesic efficacy similar to that observed with conventional dosing.
In opioid-tolerant patients with pain from malignancy, most patients were studied with a bolus size of 1-3 mg, a lockout of six minutes, and self-administered at a rate of 3-10 mg/h. In a minority of cases, patients were studied using subcutaneous route of administration, and in such cases a bolus size of 10 mg was used with a lockout of 30 minutes. PCA analgesia was rated as effective as conventional therapy by both patients and physicians.
Individualization of Dosage
The mean morphine self-administration rate observed in controlled clinical trials ranged from 1-10 mg/h, depending on the nature of the pain, the degree of opioid tolerance developed by the patient, and the individual patient factors. Most patients will achieve adequate analgesia with a 1 mg bolus and a six minute lockout, although patients with a high degree of opioid tolerance may require a larger bolus size to be comfortable without excessively frequent triggering of the device. In such patients, a bolus size of 2-3 mg is usually adequate, although up to a 5 mg bolus has been used in opioid-tolerant patients in some studies. Although the lockout interval may be varied, most investigators have left it at 6 minutes to facilitate easy calculation of the maximal dosing rate.
For opioid-naive patients, the combination of dosing rate and lockout should not permit a maximal dosing rate greater than 10 mg/h (1 mg possible every 6 minutes), while for opioid-tolerant patients maximal dosing rates up to 30 mg/h are common (3 mg every 6 minutes) and greater rates may be needed in selected patients.

INDICATIONS AND USAGE
Preservative-free Morphine Sulfate Injection is indicated for the management of pain where use of an opioid analgesic by PCA is appropriate. It was developed for administration via a compatible Hospira infusion device.

CONTRAINDICATIONS
The only absolute contraindication for *Preservative-free* Morphine Sulfate Injection is allergy to morphine or other opiates. Relative contraindications to its use are acute bronchial asthma and upper airway obstruction (see PRECAUTIONS).

WARNINGS
NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR USE IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS AND WHENEVER MORPHINE THERAPY IS BEING INITIATED.
Intravenous *Preservative-free* Morphine Sulfate Injection should be used only by those familiar with managing respiratory depression. Rapid intravenous administration may result in chest wall rigidity. Morphine sulfate may be habit forming. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS
PCA Analgesia:
Although self-administration of opioids by PCA may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.
Use in Patients with Increased Intracranial Pressure or with Head Injury:*Preservative-free* Morphine Sulfate Injection, USP, should be used with extreme caution in patients with increased intracranial pressure or with head injury. Pupillary changes (miosis) from morphine may obscure the existence, extent, and course of intracranial pathology. Clinicians should maintain a high index of suspicion for adverse drug reactions when evaluating altered mental status in patients receiving this treatment.
Use in Chronic Pulmonary Disease:
Care is urged in using this drug in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis, or paralysis of the phrenic nerve). *Preservative-free* Morphine Sulfate Injection, USP, should not be given in cases of chronic asthma, upper airway obstruction, or in any other chronic pulmonary disorder without due consideration of the known risk of acute respiratory failure following morphine administration in such patients.
Use in Hepatic or Renal Disease:
The elimination half-life of morphine may be prolonged in patients with reduced metabolic rates and with hepatic and/or renal dysfunction. Hence, care should be exercised in administering morphine to patients with these conditions, since high blood morphine levels, due to reduced clearance, may take several days to develop.

Use in Patients with Disorders of the Biliary Tract:
Care should be exercised in patients with disorders of the biliary tract because circulating morphine may induce smooth muscle hypertonicity resulting in biliary colic.

Use with Other Central Nervous System Depressants:
The depressant effects of morphine sulfate are potentiated by the presence of other CNS depressants such as alcohol, sedatives or antihistaminics. The minimum effective dose of such agents should be chosen for patients who are receiving PCA morphine to minimize the risk of respiratory depression.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy Category C:
Morphine sulfate is not teratogenic in rats at 35 mg/kg/day (thirty-five times the usual human dose), but does result in increased pup mortality and growth retardation at doses that narcotize the animal (> 10 mg/kg/day, ten times the usual human dose). *Preservative-free* Morphine Sulfate Injection should only be given to pregnant women when clearly needed and means are at hand to manage the delivery and perinatal care of the opiate-dependent infant.

Labor and Delivery:
Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

Nursing Mothers:
Morphine is excreted in maternal milk in amounts that may cause sedation of a nursing infant. Use in nursing mothers should be individualized based on the clinical situation.

Pediatric Use:
Adequate studies, to establish the safety and effectiveness of PCA-administered morphine in children, have not been performed, and usagein this population is not recommended.

Geriatric Use:
The pharmacodynamic effects of morphine in the aged are more variable than in the younger population. Patients will vary widely in the effective initial dose, rate of development of tolerance, and the frequency and magnitude of associated adverse effects as the dose is increased.

ADVERSE REACTIONS
The most serious side effect is respiratory depression (see WARNINGS). Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. The depression may be severe and could require intervention (see WARNINGS and OVERDOSAGE).
While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously. Dysphoric reactions may occur after any size dose and toxic psychoses have been reported.
Constipation: Constipation is frequently encountered during PCA-administration of morphine; this can usually be managed by conventional therapy.
Other side effects include: dizziness, euphoria, anxiety, depression of cough reflex, interference with thermal regulation, and oliguria. Evidence of histamine release such as urticaria, wheals, and/or local tissue irritation may occur.

DRUG ABUSE AND DEPENDENCE
Morphine sulfate is a Schedule II narcotic under the United States Controlled Substance Act (21 U.S.C. 801-886).
Morphine is the most commonly cited prototype for narcotic substances that possess an addiction-forming or addiction-sustaining liability. All patients are at risk for developing a dependence to morphine. As with all potent opioids which are μ-agonists, tolerance as well as psychological and physical dependence to morphine may develop irrespective of the route of administration (intravenous, intramuscular, intrathecal, epidural or oral). Individuals with a prior history of opioid or other substance abuse or dependence, being more apt to respond to the euphorogenic and reinforcing properties of morphine, would be considered to be at greater risk.
Withdrawal symptoms may occur when morphine is discontinued abruptly or upon administration of a narcotic antagonist.

OVERDOSAGE
Overdosage of morphine is characterized by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center, or as the result of hypoxia, primary attention should

be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted, or controlled, ventilation. The narcotic antagonist, naloxone, is a specific antidote. An initial dose of 0.4 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of narcotic-induced, or partial narcotic-induced, toxicity should be questioned. Intramuscular or subcutaneous administration may be used if the intravenous route is not available.

DOSAGE AND ADMINISTRATION

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE HOSPIRA INFUSION DEVICE BEFORE PRESCRIBING PRESERVATIVE-FREE MORPHINE SULFATE INJECTION, USP.

Preservative-free Morphine Sulfate Injection was developed for intravenous administration with a compatible Hospira infusion device.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate.

Intravenous Administration

For use in a compatible Hospira infusion device, dosage should be adjusted according to the severity of the pain and the response of the patient. Patients must be closely monitored because of the considerable variability in both the dosage requirements and patient response. Following are recommendations that have to be individualized for each patient.

Intravenous Adult Dosage: The usual dose for administration to adults, via a compatible Hospira infusion device, is a 1 mg bolus, with a range of 0.2 to 3 mg per incremental dose for the 0.5 mg/mL and 1 mg/mL concentrations and a range of 0.5 to 3 mg per incremental dose for the 5 mg/mL concentration. The recommended Lockout Interval is 6 minutes. The physician may adjust the dosage either upward or downward (see INDIVIDUALIZATION OF DOSAGE); depending on patient response. Occasionally, it may be necessary to exceed the usual dosage in cases of exceptionally severe pain or in those patients who become tolerant.

SAFETY AND HANDLING INSTRUCTIONS

Preservative-free Morphine Sulfate Injection is supplied in sealed PCA vials. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water. Each vial of *Preservative-free* Morphine Sulfate Injection contains a potent narcotic which has been associated with abuse and dependence among health care providers. Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic. *Preservative-free* Morphine Sulfate Injection should be subject to rigid accounting, rigorous control of wastage and restricted access.

HOW SUPPLIED

Preservative-free Morphine Sulfate Injection, USP, is supplied in single-dose 30 mL PCA vials as follows:

List No.	Concentration (mg/mL)	Total Morphine (mg/30mL)
2028	0.5	15
2029	1	30
6028	5	150

This vial is only for use with a compatible Hospira PCA pump set with injector and a compatible Hospira infusion device (see directions for use supplied with the set or infuser).

NOTE: Vial injector and PCA set are sold separately.

CONTAINS NO PRESERVATIVES. DISCARD UNUSED PORTION. DO NOT HEAT-STERILIZE.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing. Protect from light. Store in carton until time of use.

Revised: April, 2006

 EN-1179 Printed in USA

HOSPIRA, INC., LAKE FOREST, IL 60045 USA